SUMMARY

I have attempted to indicate the theoretical basis upon which the treatment of irregular uterine haemorrhage rests. The evidence is very strong that a large proportion of cases are determined by a disturbance of ovarian function, although it is impossible to say whether the majority are primarily ovarian in origin. No claim is made that modern treatment is all that can be desired; indeed, the methods available are, generally speaking, very primitive. One is conscious of two main deficiencies: the first is a lack of a biochemical method to determine with precision the amount by which the circulating hormones depart from the normal; the second is the absence of standardized hormones of high concentration. At the present day we are as yet only hovering at the fringe of a complete understanding of these ovarian abnormalities. In the future it is more than probable that organotherapy will be the method of choice in the treatment of all cases of this kind.

PRIMARY INTRATHORACIC NEW GROWTH

OBSERVATIONS ON FIFTY CASES EXAMINED
BRONCHOSCOPICALLY

BY

H. V. MORLOCK, M.C., M.D., M.R.C.P.

ASSISTANT PHYSICIAN, MILLER GENERAL AND HAMPSTEAD GENERAL
HOSPITALS; PHYSICIAN TO OUT-PATIENTS, CITY OF LONDON
HOSPITAL, VICTORIA PARK

AND

A. J. SCOTT PINCHIN, M.D., F.R.C.P.

PHYSICIAN, CITY OF LONDON HOSPITAL, VICTORIA PARK, WEST
LONDON HOSPITAL, AND HAMPSTEAD GENERAL HOSPITAL

All writers are agreed that there is a real increase in the incidence of thoracic neoplasms, and in this connexion the following figures, published by Dr. Gloyne from the records of necropsies at Victoria Park Hospital, are of interest. He makes a comparison of lung new growths in two ten-year periods, omitting the war years:

	1904-13	1921-30
Mediastinal (oat-celled)	16	38
Lungs and pleura	4	43

It is apparent from these figures that not only have the growths increased from twenty in the first period to eighty-one in the second, but, whereas in the first period the oat-celled type had a frequency four times greater than growths in lung and pleura, in the second period the latter exceeds the former. At the same hospital, for the years 1931 and 1932, there have been thirty-five necropsies on intrathoracic growth. If we compare the yearly average for these separate periods the picture is even more striking:

	Mediastinal (oat-celled)	Lungs and Pleura	Proportion
1904-13	1.6 per year	0.4 per year	4 to 1
1921-30	3.8 ..	4.3 ..	1 to 1 (approx.)
1931-32	6.5 ..	11.0 ..	1 to 2 (approx.)

Thus the oat-celled type of growth in twenty-five years has increased about four times, the growths of lung and pleura over twenty-seven times.

CLASSIFICATION OF TUMOURS

In the bronchoscope we have an instrument for the visual examination of the bronchi, and its value in the diagnosis of pulmonary neoplasm will be dependent on the frequency with which this disease gives rise to changes in the bronchial tree, and also in what stage of the disease

these bronchial changes are produced. It is generally accepted that malignant intrathoracic growths fall into four groups:

1. Growths of the mediastinal glands (in the older textbooks known as lymphosarcoma, now generally referred to as oat-celled carcinoma).
2. Pleural growths.
3. Bronchial carcinoma (large and single or small and multiple).
4. Pulmonary carcinoma.

Group 1 would appear to be composed of two types: true lymphosarcoma (rare), and the oat-celled growth, which is usually regarded as of primary bronchial origin with early (?) and extreme glandular involvement—in this case the oat-celled growth should be included in the bronchogenetic group. There is no real dividing line between Groups 3 and 4. Some pathologists surmise a different site of origin—for example, mucous gland, alveolar wall, bronchial wall; others are inclined to class all cases of these groups as bronchial in origin, and they explain the difference in the histological picture by assuming that the growth begins in different cases at different levels of the bronchial mucosa, and that a pulmonary carcinoma is merely one in which extension has taken place from a bronchus. From the clinical and bronchoscopic point of view these distinctions are of little importance, as in the two common types—that is, the oat-celled and large bronchus type (the others being of great rarity)—the ulceration commences, or appears to commence, in the large bronchi fairly close to the carina. It is therefore in these two types that the bronchoscope will give valuable diagnostic information. In cases of carcinoma arising in the secondary bronchi, in the parenchyma of the lung, or in the pleura, no bronchoscopic evidence is found until the glands become involved at the root, or secondary extension takes place.

The cytological problem, as mentioned above, is a difficult one, and if this is true of the post-mortem specimen it is easy to understand the difficult position in which the histologist is placed when asked to report on the small portions of tissue, often crushed by the forceps, which one is able to obtain for section during life. It is probably on this account that one has experienced occasional shocks in the endeavour made to differentiate the type of growth by the bronchoscopic appearances and the clinical findings. Nevertheless, the findings generally admit of the following data.

Oat-celled Type.—This appears to arise in the deep layers of the mucosa; the spread is rapid to the lymphatics, and enormous enlargement of the mediastinal glands takes place. Bronchoscopically in the oat-celled type the mucosa is infiltrated and ulcerated, little raised nodules are seen, whitish in colour as compared with the normal mucous membranes, but polypoid formation is rare, though occasionally deeper in the bronchial tree there may be some tendency to occlusion. In association with this type of ulceration evidence of glandular enlargement is seen. There may be some bulging into the trachea, widening and deformation of the carina, and scabbard-shaped bronchi. Section can usually only be obtained with a punch forceps.

Bronchial Type.—These tumours appear to arise in the superficial layers of the bronchus. There is a tendency to spread into the lumen rather than to the lymphatics; glandular enlargement is rare, and the clinical signs are, as we have stated elsewhere, somewhat pleomorphic, but dependent usually on the bronchial obstruction. Bronchoscopically there is usually no evidence of glandular enlargement, the carina is not widened, but may be dragged over if there is collapse of lung; the bronchus is seen to be partially or completely blocked by a polypoid

mass, which can be removed easily with forceps. In both types the position is usually in main stem bronchus, a short distance below the bifurcation. Clinically the type is usually fairly clear-cut: rarely one may see cases of the bronchial type in which masses of gland in the mediastinum are found, or the oat-celled type in which glands are not found, but we suspect that some of these aberrant cases have been due to difficulties in the histology. For convenience of description one might possibly divide these types into:

Centrifugal (the oat-celled type with the greater tendency to glandular involvement), and

Centripetal (the type marked by spread into lumen rather than at an early stage to glands).

The importance of differentiation in these two types lies in the fact that in the centrifugal type the early involvement of glands renders treatment of little value. In the centripetal type the result of treatment should be more valuable if the case is obtained in time. Of the thirty-five cases coming to necropsy in 1931 and 1932 the average age in both groups is 52, the lowest age 34, the highest 63. The dangerous age appears to be 45 to 55. The bronchoscopic examination is the safest and surest method of examination and proof. We have recently seen a man whose bronchial tree was "lipiodolled" and declared normal, and who was dead of a bronchial carcinoma in two months.

RESULTS OF BRONCHOSCOPY

Of the fifty cases we have analysed many were sent with an incorrect diagnosis; others had very few symptoms at all, and yet only one was a case in which much hope could be held out from treatment. Whether or no it may be possible to improve our ideas of the symptomatology, these cases, especially the bronchial type, must be seen at an earlier stage for success in treatment. It is possible that, if the practitioner reviewed the past history of cases found to have this disease, he might be able to remember some points which would be an aid in the earlier diagnosis of this condition, and in getting the patient for bronchoscopy at a period when it is possible to do something effective in the way of treatment. Our submission of the value of the bronchoscope is borne out by the examination we have made by this method on fifty cases of pulmonary growth which have been under our care or referred to us for examination during the last two years. In all of them we have been able to make or confirm a diagnosis. In 62 per cent. this was done by removing a piece for section; in the remaining 38 per cent. direct evidence of growth was found as indicated by ulceration in 30 per cent., and observation of the effects produced on the bronchial tree by pressure from without in 8 per cent. As a rule the protrusion into the wall of bronchus or trachea in these cases was covered by a normal mucous membrane, and was not sufficient to cause a complete block of the main bronchus, but usually to give some obstruction to the passage of the bronchoscope.

In two other cases (apart from the fifty) in which we presumed that the findings were diagnostic of new growths, we were wrong, the patients being alive and well and *in statu quo* two years later. It is interesting to note that both these cases were examined with the Haslinger bronchoscope, before we had perfected our telescopic instrument. In the one case no ulceration was seen, but, owing to the distortion of the left upper lobe bronchus, it was considered suspicious. This, it would appear, was caused by fibrosis.

From these figures it will be seen that in the first fifty-two cases which we examined bronchoscopically for the disease positive proof by section was obtained in 62 per cent., and in the rest bronchoscopic indications which have proved erroneous in only two cases.

COURSE OF THE DISEASE

To appreciate fully the value of the bronchoscope in the diagnosis of new growth of the lung we should follow as accurately as we can the course of the disease.

Early Signs

It is probable that the centripetal type appears first as a small growth, warty or polypoid, in the bronchial mucous membrane. It would appear that an occasional fortunate individual has been caught at this stage with cure as a result. Usually, if it gives any symptom at all, it will only be an irritating cough; when slightly larger, possibly a localized wheeze. Otherwise physical and radiological examination is negative. Only the bronchoscope can reveal the condition. As growth continues it may give rise comparatively early to slight haemoptyses. Again physical and radiological examination is negative. We have examined forty-two cases of haemoptysis with no radiological or pathological evidence available, and in five cases have found neoplasm.

In the case of a male, aged 50, who had had repeated haemoptyses over twenty years, physical and radiological examinations were negative. Bronchoscopy showed a polyp between the upper and middle lobe bronchi. A section was reported as bronchial carcinoma. In view of the long history this diagnosis is questionable, although cases are reported of benign growth being present for years before becoming malignant.

In this early stage the glands around the bifurcation from the main bronchi may become involved, though, as stated above, this is more common in the centrifugal type, in which this kind of history is not usually obtained: although at this stage the involvement will give no radiological evidence a bulge in the main stem bronchus may often be seen.

In a male, aged 60, with a six months' history of cough, dyspnoea, and loss of weight, the physical signs were increase in substernal dullness to the left and weak air entry into the left lower lobe. Skiagram showed a dense shadow in the left hilar region. On bronchoscopic examination no growth was seen, but the left main stem bronchus was distorted by a bulging in of the external wall just below the opening of the upper lobe bronchus.

Bronchial Occlusion

The next stage is occlusion of a bronchus by a growth, which causes collapse of the lobe supplied by the bronchus, and also gives rise to clinical signs and symptoms frequently mistaken for pneumonia. At this stage a definite radiological picture of a collapsed lobe is produced, and the differential diagnosis of bronchiectasis and mediastinal effusion ruled out. A lipiodol injection and skiagram will often show a blocked bronchus, but it must be remembered that the demonstration of a blocked bronchus by means of lipiodol does not necessarily mean that the block is caused by new growth. We have seen such a picture produced by fibrosis, tuberculosis, or broncholiths.

In a male, aged 45 years, with repeated haemoptysis, physical signs and radiological reports were negative. A skiagram after lipiodol injection revealed a partial "hold up" of the lipiodol in the right lower lobe. Bronchoscopic examination showed the cause of the lipiodol "hold up" to be a broncholith. At necropsy following a fatal haemorrhage some time later the presence of the broncholith was confirmed. On reconsideration of the original skiagram the shadow cast by the broncholith could be distinguished from the shadow of the fibrosis around it.

The following are examples of collapse of a lobe or lung due to a blocked bronchus by a neoplasm.

A male, aged 40. Three months previous to admission he developed pneumonia, from which he made a protracted recovery. On examination there were signs of collapse of the

right lower lobe, confirmed by a skiagram. After lipiodol skiagram showed a "hold up" of lipiodol at the lower lobe. Bronchoscopic examination showed a new growth. A section removed proved to be an oat-celled carcinoma.

A male, aged 34, had for some indefinite period complained of cough. Three weeks before admission he complained of pain in the left chest and dyspnoea. Physical signs were those of collapse of the whole of the left lung. Bronchoscopic examination revealed a mass blocking both upper and lower left bronchi. Section showed an oat-celled carcinoma. Radium inserted by the bronchoscope has caused the intrabronchial growth to diminish so much in size that both upper and lower lobes are now re-expanded.

In some cases of collapsed lobe due to a neoplasm the skiagram, after a lipiodol injection, may fail to show the lipiodol "hold up," because the lipiodol has entered the bronchi anteriorly and posteriorly to the bronchus which is blocked, and has thus reached the distal bronchi, and obscured on the skiagram the lipiodol which is held up.

A male, aged 52 years, gave a twelve months' history of pain and cough, with slight haemoptysis. Physical signs included partial collapse at the right lower lobe, confirmed by skiagram. After lipiodol the skiagram showed the lipiodol to have entered the distal bronchi, and no "hold up" was visible. Bronchoscopic examination showed a new growth obstructing the internal division of the lower lobe bronchus, while the anterior and posterior division were patent. Section showed a bronchial carcinoma.

Pleural Effusion

An effusion may appear coincident with the collapse, or even before. The physical and radiological signs are those of an effusion, and nothing in either examination may suggest a new growth. Some help may be obtained by pathological examination of the fluid or by radiological examination after air replacement. Neither method is certain, but bronchoscopic examination may give a proven diagnosis.

A male, aged 34, had physical signs and radiological evidence of effusion at the left base. The patient's general appearance did not suggest tuberculosis. Bronchoscopic examination was thought worth while, and revealed a new growth blocking the lower lobe. Section showed an oat-celled carcinoma.

In another case the pathological examination of pleural exudate withdrawn from a young man was reported as diagnostically suggestive of neoplasm. Nothing else suggested new growth. Bronchoscopic examination was negative. (Here it must be remembered that a negative finding has not the value of a positive one; the growth might be in a second division bronchus, or might even be an alveolar growth.) The patient has made a perfect recovery from the "simple effusion."

Suppuration

The next pathological stage in the development of the new growth is suppuration in the lung and bronchi behind the obstructed or partially obstructed bronchus. At this stage the physical signs and symptoms are those of pulmonary suppuration. There are certain points of difference in the x-ray which may point to new growth as the cause, but occasionally lipiodol examination will show up a bronchiectatic condition or abscess without giving a hint that the causative factor is new growth. All cases of pulmonary suppuration must be bronchoscoped to ascertain the cause: we have found various causes at different times, from half a coat button to daughter hydatid cysts.

A male, aged 55, complained of coughing up blood and foul sputum for eighteen months. Physical signs and the x-ray suggested an abscess in the left middle zone. A skiagram after lipiodol gave no further help. Bronchoscopic examination revealed a polypoid growth partially obstructing the upper lobe bronchus.

A female, aged 23 years, gave a history of eighteen months' coughing up blood and foul sputum. The physical signs and

skiagram suggested bronchiectasis at the right base. Skiagram after lipiodol confirmed this. Bronchoscopic examination showed a polypoid growth partially obstructing one of the lower lobe bronchi.

THE VALUE OF BRONCHOSCOPY

From the above description of the mode of development and symptomatology of the bronchial carcinoma it will be seen that the bronchoscope must play the paramount part in diagnosis, and, though in the advanced cases an old pattern instrument is sufficient, in the earliest type of case—which one hopes to get in the future, with a greater knowledge of the diagnostic feature of the earlier stages of the disease—aids to vision in the way of better illumination and telescopic attachment such as we have described will have to be used. The destructive argument might be raised that, *early* diagnosis of the disease being at present impossible—and at the stage when it does become possible treatment has ceased to be of value—confirmation of diagnosis at this stage is of little use. Though this may in part be true, the fact remains that if ever a successful treatment is to be evolved the experimental treatment must be done on those cases which, though not early in the pathological sense, are yet earlier than those cases diagnosed in the past. It is only since the bronchoscope has been used in this diagnostic work that the condition has been diagnosed with absolute certainty (by macroscopic section), whereas previously certainty had to wait on the appearance of secondary glands or deposits elsewhere. With regard to the other varieties of intrathoracic new growth (excluding pleural growth)—sarcoma and alveolar carcinoma—the bronchoscope can only give information if the growth has reached the bronchial walls, either deforming their contour or ulcerating or infiltrating them. At this stage the disease has advanced beyond hope from treatment, though confirmation of the diagnosis is obtained.

TREATMENT

As regards treatment, deep therapy has been disappointing. A patient with alveolar carcinoma after deep therapy spat up most of his growth leaving a cavity the size of an orange, but he shortly developed secondaries. The glandular type, whether oat-celled cancer or lymphosarcoma, seems to have a similar tendency to dissemination after treatment. One case developed a secondary in the eye (a very rare condition), while in others we have seen the most extensive dissemination in this disease, where the metastases are not usually wide if untreated. The bronchial type seems little influenced. The radium bomb, we understand, has also not proved its value. Pituitary and theelin has proved on several patients quite useless. The best hope seems to lie in radium or radon applied locally. We have had a number of patients whom we have treated in this way, but the method is still too much in the experimental stage for there to be reports in any sense on its efficacy. It appears, however, that there is some hope in this direction. If the cases can be obtained earlier probably much could be done. In the centripetal type of case somewhat more advanced lobectomy is hopeful if the growth is low enough in the bronchial tree, as is commonly *not* the case. Nevertheless, it is difficult to advise a patient who at this stage usually appears to be in perfect health to submit to an operation of high mortality risk, though the surgical figures for lobectomy are rapidly improving to a stage when one would feel justified in advising it.

SOME CONCLUSIONS

Of the fifty cases on which these observations have been made from the bronchoscopic findings the following aetiological points are of interest.

Only four of the cases (8 per cent.) were in women, and of these one was probably primary pleural, one a haemangio-endothelioma, one of the multiple bronchial type, and only one of the common type of bronchial carcinoma.

In no one case was the disease found in a patient of the Jewish race. As the City of London Chest Hospital is in the centre of a district in which the Jewish population is large this is somewhat striking.

The age incidence is as follows:

Years	Cases	Percentage
21-30	5	10
31-40	2	4
41-50	16	32
51-60	21	42
61-70	6	12

At the Centenary Meeting of the B.M.A. last year some laryngologists expressed the opinion that bronchoscopy should be in the hands of the laryngologists. To us it appears that the bronchi are so obviously the field of the chest physician that though every chest physician should not be a bronchoscopist, the bronchoscopist may most advisedly be a chest physician.

We wish to acknowledge with gratitude the help of Dr. Roodhouse Gloyne and Dr. D. S. Page for the pathological examinations, which have entailed a large amount of work.

EXPERIENCES WITH PROTEOSE IN THE TREATMENT OF DISEASES OF THE SKIN

BY

NORMAN BURGESS, M.A., M.D.CAMB., M.R.C.P.

PHYSICIAN IN CHARGE OF THE SKIN AND LIGHT DEPARTMENTS, BRISTOL
GENERAL HOSPITAL; CLINICAL LECTURER IN DISEASES OF
THE SKIN, UNIVERSITY OF BRISTOL

It is somewhat surprising that although over four years have elapsed since Barber and Oriel produced their first paper¹ on the discovery of a urinary proteose, which in cases of allergy appears to be combined with an antigen, little has been published on this subject except by the original authors.^{2,3,4} Beyond correspondence by Freeman⁵ and myself,⁶ and short papers by Lyon, Percival, and Stewart⁷ and by Eichenlaub,⁸ the work does not seem to have been followed up to any great extent by dermatologists, although many claims have been made for the results of treatment by proteose in cutaneous diseases. The present paper forms a part of a larger investigation carried out for the British Medical Association as their Research Scholar for 1931-2. Some of the results were communicated to the British Association of Dermatology and Syphilology at the annual meetings in 1932.

It will be remembered that Barber and Oriel make the following statements:

1. That a proteose may be extracted from the urine by ether, and precipitated from the ether extract by alcohol.
2. That although proteose is present in small quantities in health, it is very much increased in cases of allergy.
3. In cases of urticaria and asthma the proteose is found in large quantities in urine passed during the attack, while it is small in amount or absent between the attacks.
4. Solutions of the proteose obtained in cases of allergy, when injected intradermally, produce specific skin reactions in the patient from whom the proteose was obtained; sometimes they produce reactions in those suffering from the same condition, but not in normal persons.
5. This sensitivity may be transferred by the Prausnitz-Kustner method.
6. In cases of epidermal sensitization, positive reactions may be obtained by application of the proteose to the surface of the skin by means of a patch test.

7. Comparatively large doses of proteose injected intradermally cause an exacerbation of the symptoms, while minute doses over a long period lead to a cure of the condition.

Freeman has been unable to confirm these results, while Lyon, Percival, and Stewart found that twenty-one out of twenty-five proteoses which they prepared gave positive reactions not only in the patients from whom they were prepared, but also in normal persons and in those suffering from various skin diseases. They also found that proteose prepared from a patient suffering from the eczema-asthma syndrome gave a negative reaction in the patient from whom it was prepared, but positive reactions in other persons. A case of angioneurotic oedema failed to respond to its own proteose, but gave a positive reaction to a proteose prepared from a case of chronic urticaria. Two cases of asthma in which the proteose content of the urine was very high gave negative reactions to their own proteoses. They conclude that the peculiarity of proteose lies not in its specificity, but in its property of producing a local inflammation of great intensity in a proportion of individuals.

Eichenlaub treated eighteen patients suffering from skin diseases with proteose. All of the patients who gave definitely positive skin reactions—that is, ten of the eighteen patients—appeared to receive some benefit from the treatment. Only one of the other eight persons improved. Cases in which complete failure was observed gave no local or general reactions to their proteoses, but a case of psoriasis derived benefit from the treatment, although a positive skin reaction was not obtained. He came to the following conclusions as the result of his work:

1. It has been possible to confirm the specificity of the antigen by (a) securing negative reactions to foreign proteose in patients who definitely reacted to their own proteoses, and (b) obtaining a positive Prausnitz-Kustner reaction in a normal person.
2. Therapeutic results have been sufficiently encouraging to warrant further trial. They have not been definite enough to confirm entirely the value of this procedure.
3. The proteose is highly active in some persons. The patient's sensitivity to each of the dilutions should be carefully determined before treatment is started.

RESULTS IN THE PRESENT SERIES

Twenty-six cases have been treated with intradermal injections of proteose. During the period of treatment local application was limited to the use of ichthyol-zinc cream, or 2 per cent. hyd. amm. and ac. salicyl. in zinc paste.

Five cases of *psoriasis* were treated, of which one cleared up completely, while two cleared up temporarily but later relapsed. Another patient was suffering from psoriasis and rheumatoid arthritis; a positive reaction was obtained on intradermal injection of 0.05 c.cm. of a 1 in 100,000 solution of proteose. After six weekly injections of 0.05 c.cm. of a 1 in 10,000,000 solution there was very considerable improvement, both in the psoriasis and in the arthritis. Following each injection there was some exacerbation of the joint pains within twenty-four hours; this patient is still under treatment. Another patient showed considerable improvement while undergoing the treatment, but although the eruption faded considerably it did not entirely clear up.

Eight cases of *chronic eczema* were treated. Of these, five cleared up completely and have not relapsed, one cleared up completely but relapsed in a few months, while two showed some improvement but did not completely clear up. One of the cases had a severe reaction twenty-four hours after an injection of a 1 in 10,000 solution of proteose. There was an exacerbation of the skin eruption and a considerable degree of general malaise.